PATENT

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Roberto Malinow, *et al.*

Serial No.: 09/353,126
Filed: July 14, 1999

For: **DIAGNOSTIC METHODS FOR DRUG SCREENING FOR ALZHEIMER'S DISEASE**

) Examiner: S. L. Turner
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) Art Unit: 1647
)
) **CLEAN COPY OF CLAIMS**
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BOX AF
Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

The following is the text of the pending claims including amendments shown on the attached "Version with Markings to Show Changes Made".

IN THE CLAIMS:

1. (Amended) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting hippocampal cells comprising a presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells to tetanic stimulation; and

determining the effect of said candidate drug on the synaptic potentiation of said mutant hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

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Signature: [signature]

Printed Name: Jeffrey M. Libby

3. (Reiterated) The method according to Claim 1, wherein mouse hippocampal tissue slices comprise said mutant hippocampal cells.

4. (Reiterated) The method according to Claim 1, wherein said enhanced synaptic potentiation is a result of a change in the $GABA_A$ receptor pathway.

5. (Amended) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting hippocampal cells comprising a presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to a tetanic stimulus;

measuring changes in potentiation with time of the mutant hippocampal cells and wild-type hippocampal cells and comparing the effect of said candidate drug on the synaptic potentiation of said mutant hippocampal cells as compared to the observed synaptic potentiation of said wild-type hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells as compared to the synaptic potentiation of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

6. (Amended) A method for determining whether a mutation in hippocampal cells acts on a common pathway with a $GABA_A$ receptor antagonist, said method comprising:

contacting hippocampal cells comprising a presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a $GABA_A$ receptor antagonist;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to tetanic stimulation; and

measuring changes in synaptic potentiation with time of said mutant hippocampal cells and said wild-type hippocampal cells and comparing the effect of said $GABA_A$ receptor

antagonist on said mutant hippocampal cells and said wild-type hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells without a significant change in the synaptic potentiation of the wild-type cells is indicative of the mutation acting on a common pathway with said $GABA_A$ receptor antagonist.

7. (Reiterated) The method according to Claim 5, wherein said candidate drug is present with said wild-type hippocampal cells.

8. (Amended) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting hippocampal cells comprising a presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to a tetanic stimulus at a first potential of glutamate currents and a second potential of $GABA_A$ currents;

measuring the synaptic response at each of the first and second potentials for said mutant hippocampal cells and said wild-type hippocampal cells and comparing the effect of said candidate drug on said mutant hippocampal cells and said wild-type hippocampal cells;

wherein a reduction in the enhanced synaptic response of the mutant hippocampal cells without a significant change in the synaptic response of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

9. (Amended) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting mouse hippocampal cells comprising a presenilin-1 gene mutation and having enhanced synaptic potentiation upon tetanic stimulation as compared to wild-type hippocampal cells, with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to tetanic stimulation; and

comparing the effect of said candidate drug on said mutant hippocampal cells and said wild-type hippocampal cells upon tetanic stimulation;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells without a significant change in the synaptic potentiation of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

10. (Reiterated) Slices of mouse hippocampal tissue containing cells having a mutation in a presenilin gene combined with a candidate drug that is not an antibody.

11. (Reiterated) Slices of mouse hippocampal tissue containing cells according to Claim 10, after tetanic stimulation.

12. (Reiterated) Slices of mouse hippocampal tissue containing cells according to Claim 10, wherein said mutation is a PS-1 Δ9 mutation.

13. (Reiterated) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting slices of mouse hippocampal tissue containing cells, having a PS-1 Δ9 mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells to tetanic stimulation; and

determining the effect of said candidate drug on the synaptic potentiation of said mutant hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

14. (New) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting hippocampal cells comprising a PS-1 Δ9 presenilin gene mutation wherein said hippocampal cells have enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells to tetanic stimulation; and

determining the effect of said candidate drug on the synaptic potentiation of said mutant hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

15. (New) The method according to Claim 14, wherein mouse hippocampal tissue slices comprise said mutant hippocampal cells.

16. (New) The method according to Claim 14, wherein said enhanced synaptic potentiation is a result of a change in the $GABA_A$ receptor pathway.

17. (New) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting hippocampal cells comprising a PS-1 Δ9 presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to a tetanic stimulus;

measuring changes in potentiation with time of the mutant hippocampal cells and wild-type hippocampal cells and comparing the effect of said candidate drug on the synaptic potentiation of said mutant hippocampal cells as compared to the observed synaptic potentiation of said wild-type hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells as compared to the synaptic potentiation of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

18. (New) A method for determining whether a mutation in hippocampal cells acts on a common pathway with a $GABA_A$ receptor antagonist, said method comprising:

contacting hippocampal cells comprising a PS-1 Δ9 presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a $GABA_A$ receptor antagonist;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to tetanic stimulation; and

measuring changes in synaptic potentiation with time of said mutant hippocampal cells and said wild-type hippocampal cells and comparing the effect of said $GABA_A$ receptor antagonist on said mutant hippocampal cells and said wild-type hippocampal cells;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells without a significant change in the synaptic potentiation of the wild-type cells is indicative of the mutation acting on a common pathway with said $GABA_A$ receptor antagonist.

19. (New) The method according to Claim 18, wherein said candidate drug is present with said wild-type hippocampal cells.

20. (New) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting hippocampal cells comprising a PS-1 Δ9 presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to a tetanic stimulus at a first potential of glutamate currents and a second potential of $GABA_A$ currents;

measuring the synaptic response at each of the first and second potentials for said mutant hippocampal cells and said wild-type hippocampal cells and comparing the effect of said candidate drug on said mutant hippocampal cells and said wild-type hippocampal cells;

wherein a reduction in the enhanced synaptic response of the mutant hippocampal cells without a significant change in the synaptic response of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

21. (New) A method for screening for drugs for the treatment of Alzheimer's disease, said method comprising:

contacting mouse hippocampal cells comprising a PS-1 Δ9 presenilin-1 gene mutation and having enhanced synaptic potentiation upon tetanic stimulation as compared to wild-type hippocampal cells, with a candidate drug;

subjecting said mutant hippocampal cells and said wild-type hippocampal cells to tetanic stimulation; and

comparing the effect of said candidate drug on said mutant hippocampal cells and said wild-type hippocampal cells upon tetanic stimulation;

wherein a reduction in the enhanced synaptic potentiation of the mutant hippocampal cells without a significant change in the synaptic potentiation of the wild-type cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

22. (New) Slices of mouse hippocampal tissue containing cells having a mutation in a presenilin gene combined with a candidate drug that suppresses intracellular calcium rise in said cells.

23. (New) Slices of mouse hippocampal tissue containing cells according to Claim 22, after tetanic stimulation.

24. (New) Slices of mouse hippocampal tissue containing cells having a PS-1 Δ9 mutation in a presenilin gene combined with a candidate drug that suppresses intracellular calcium rise in said cells.

25. (New) Slices of mouse hippocampal tissue containing cells according to Claim 24, after tetanic stimulation.

26. (New) A method for screening for a candidate drug that suppresses intracellular calcium rise in slices of mouse hippocampal tissue containing cells having a PS-1 Δ9 mutation in a presenilin gene combined with a candidate drug for the treatment of Alzheimer's disease, said method comprising:

contacting hippocampal cells comprising a presenilin gene mutation and having enhanced synaptic potentiation upon stimulation as compared to wild-type hippocampal cells with a candidate drug that suppresses intracellular calcium rise in said cells;

subjecting said mutant hippocampal cells to tetanic stimulation; and

determining the effect of said candidate drug on the ratio of peak inhibitory to excitory responses;

wherein an enhanced said ratio of peak inhibitory to excitory responses in said mutant

hippocampal cells as compared to wild-type hippocampal cells is indicative of activity of a candidate drug for the treatment of Alzheimer's disease.

CONCLUSION

Should the Examiner have any questions regard the above, in order to expedite prosecution, the Examiner is invited to call the undersigned.

Respectfully submitted,

Dated: November 9, 2001

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